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Review

Cross-talk between oxidative stress signaling and microRNA regulatory systems in carcinogenesis: Focused on gastrointestinal cancers

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ABSTRACT

Molecular mechanisms underlying development and progression of gastrointestinal (GI) cancers are mediated by both oxidative stress (OS) and microRNAs (miRNAs) involvement. Notably, OS signaling may regulate the expression of miRNAs, and miRNAs function as imperative players in OS-initiated tumors. Given the defined biological roles of both OS systems and miRNAs in GI carcinogenesis, a possible interplay between these two key cellular networks is considered. A growing body of evidence has indicated a reciprocal connection between OS signaling pathways and miRNA regulatory machines in GI cancer development and progression. Illumination of the molecular cross-talking between miRNAs and the OS would improve our pathophysiological insight into carcinogens. Also, understanding the molecular mechanisms in which these systems are reciprocally regulated may imply in future medical practice mainly GI cancer therapy. Nowadays, therapeutic strategies focusing on miRNA and OS in GI cancer treatment are increasingly delineated. Since the use of antioxidants is limited owing to the contrasting consequences of OS signaling in cancer, the discovery of OS-responsive miRNAs may provide a potential new strategy to overcome OS-mediated GI carcinogenesis. Given the possible interaction between OS and miRNAs in GI cancers, this review aimed to elucidate the existing evidence on the interaction between OS and miRNA regulatory machinery and its role in GI carcinogenesis. In this regard, we will illustrate the function of miRNAs which target OS systems during homeostasis and tumorigenesis. We also discuss the biological cross-talk between OS systems and miRNAs and corresponding cell signaling pathways.

Abbreviations: GI, gastrointestinal; OS, oxidative stress; MiRNA, microRNAs; ROS, reactive oxygen species; RISC, RNA-induced silencing complex; H_2O_2, hydrogen peroxide; OH^-, hydroxide; O_2^-, superoxide; SOD, superoxide dismutase; GPXs, glutathione peroxidase; CAT, catalase; Nrf2, NF-E2-related factor; ARE, antioxidant response element; HO1, heme oxygenase-1; NQO1, NAD(P)H quinoneoxidoreductase 1; GSTs, glutathione S-transferase; KEAP1, Kelch-like ECH-associated protein 1; CMVEC, cerebromicrovascular endothelial cell; HUVEC, human umbilical endothelial cell; SIRT1, silent mating-type information regulation 2 homolog; FOXO, forkhead box O; NF- κB, nuclear factor-κB; LDH, lactate dehydrogenase; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; PRXL2A, peroxiredoxin like 2A; hSOD2b, human manganese superoxide dismutase; TLR4, toll-like receptor 4; CRC, colorectal cancer; TFs, transcription factors; ANXA2, annexin II protein; EMT, epithelial-mesenchymal transition; iNOS, inducible nitric oxide synthase; ZBTB10, zinc finger and BTB domain containing 10; PTB1, polypyrimidine tract-binding protein 1; PKM1, pyruvate kinase muscles 1; GC, gastric cancer; T-AOC, total anti-oxidation competence; 8-OHdG, 8-oxo-deoxyguanosine; hOGG, human 8-oxoguanine DNA N-glycosylase; PDCD4, programmed cell death 4 protein; PPARγ, peroxisome proliferator-activated receptor gamma; PI3K/Akt, phosphatidylinositol 3 kinase/protein kinase B; HIF-1α, hypoxia-inducible factor-1 α; HCC, hepatocellular carcinoma; HRE, hypoxia response element; ESCC, esophageal squamus cell carcinoma; STAT3, signal transducer and activator of transcription 3; SPRY-2, sprouty homolog 2; PTEN, phosphatase and tensin homolog; BIM, bcl-2 interacting mediator; ZEB1, zinc finger E-box binding homeobox 1; KLF4, Kruppel-like factor 4; PARP1, poly(ADP-ribose) polymerase 1; MAPK, mitogen-activated protein kinase.

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1. Introduction

The gastrointestinal (GI) system-related cancers are responsible for more cancers morbidity and mortality than any other systems in the body [1]. Approximately 30 % of cancer incidence and 32 % of cancer deaths are due to GI malignancies (colorectum, stomach, liver, oesophagus and pancreas) worldwide [2]. The etiology and risk factors of GI cancers to some extent are associated with genetic background, inflammation and co-infections, obesity, liver cirrhosis, metabolic disorders, tobacco use, dietary factors and chronic oxidative stress [3,4]. Oxidative stress (OS), refers to the redox imbalance with overproduction of reactive oxygen species (ROS) above the ability of antioxidant defense [5,6]. In this regard, increasing investigations have revealed that the GI is the main place of oxidant and antioxidant occurrences [7,8]. OS-activated signaling pathways have been frequently associated with the development and progression of numerous solid malignancies, including GI cancers [9]. From the biological point of view, cancer-related OS signaling pathways are implicated as a network, as well as, interplay between OS and related genes. Non-coding RNAs, including microRNAs (miRNAs) comprise the functional players in gene regulation and have recently been demonstrated to be involved in cancer-associated OS signaling pathways. In this view, OS signaling has been revealed to regulate the expression of miRNAs that may function as imperative players in OS-derived tumors. A line of evidence suggests a reciprocal connection between OS signaling pathways and miRNA regulatory machines in GI cancer development and progression. In this review, we elucidate the interaction between OS and miRNAs and focus on biological aspects of this network signaling in GI carcinogenesis. We highlight the possible function of miRNAs which target OS systems during homeostasis and tumorigenesis and discuss the corresponding biological cross-talking and cell signaling pathways.

2. OS signaling pathway in Cancer development

Cellular metabolism usually produces ROS, indicating as the key inducers of various signaling pathways in intra- and extracellular environmental circumstances [10]. Low levels of ROS can act as a cellular signal that changes protein structure and activity through oxidizing the thiol groups of amino acids. Whilst, higher amounts of ROS may disturb cellular function by attacking lipids, proteins, and DNA [11]. OS and redox signaling have been to be involved in the cancer development, so that ROS can affect the characteristics of cancer cells and their reactivity to growth signals as well as cellular homeostasis [12]. Moreover, oxidative damage to DNA has been documented to definitely sensitize cells to cancer-associated mutations. Taken together, OS activation can promote cancer-initiated episodes and indirectly lead to cancer development [12].

3. MiRNAs regulatory systems and Cancer

MiRNAs are characterized as small non-coding RNAs of 18–23 nucleotides, which negatively regulate gene expression through targeting the mRNA [13]. MiRNA molecules are commonly transcribed by RNA polymerase II/III as immature primary miRNAs (pri-miRNAs). After a two-step processing of pri-miRNA in the nucleus by Dicer (endoribonuclease Dicer or helicase with RNase motif) and Drosha (a class 2 ribonuclease III enzyme) complexes, the mature form of miRNA is created [14]. In the cytoplasm, the mature miRNA is combined with the RNA-induced silencing complex (RISC) to act as a functional miRNA. Cytoplasmic mature functional miRNAs typically regulate the gene expression by post-transcriptionally suppressing the translation or inducing mRNA degradation by binding to 3′ untranslated region (UTR) sequence [15,16]. Notably, the miRNA database (miRBase) [17], released in June 2014, indicated the existence of approximately 2588 mature miRNAs in human. It has been estimated that miRNAs regulate ~60 % of human genes [18]. Many studies have shown that miRNAs are associated with the pathophysiology and treatment of cancers [19]. Growing evidence indicates that miRNA can involve in tumorigenesis by regulating various oncogenes and tumor suppressor genes. Cellular functions of miRNAs impact on various aspects of tumor development including cell proliferation [20], tumor growth, spread, metastatic ability [21], apoptosis [22]and angiogenesis [23]. A range of genes regulated by miRNAs has been specified to be related to tumor growth and aggressiveness [24]. In this regard, miRNA profiles of tumors can clarify patient survival and intervention respond [25,26]. A line of evidence also represents the possible ability of cell-free circulating miRNAs in the clinic as biomarkers for cancer diagnosis and prognosis [27]. Cancer-related miRNA biomarkers can even be found in biological fluids like plasma, saliva and urine, as well as amniotic and seminal fluids providing the possibility of a less-invasive monitoring [28]. MiRNA dys-regulation in cancer pathophysiology was first got attention when a cluster of miRNAs, was detected at frequently deleted sequences in malignancies [29]. Recently, more interests have concentrated on evaluating the changes in miRNA expression pattern to detect novel cancer biomarkers and therapeutic strategies [30].

4. Interaction of miRNAs and OS in Cancer

Since both miRNAs and OS are affected/ dysregulated in pathological circumstances, including cancer, it is critical to find out the biological interplay between miRNAs and OS. Notably, ROS, including hydrogen peroxide (H_2O_2), hydroxide (OH^-) and superoxide (O_2^-) cause damage to cell lipids, proteins, RNA, and DNA [31]. To maintain redox homeostasis, the body has an antioxidant defense system composed of various enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPXs), and catalase (CAT) to scavenge ROS. One of the important functions of ROS is stimulating the NF-E2-related factor (Nrf2)-mediated activation of an antioxidant response element (ARE) to defend cells and body against OS [32]. Nrf2 was confirmed to transcriptionally regulate the expression of multiple critical enzymes of anti-oxidative defense [33,34]. The activation of Nrf2-ARE pathway, in turn, leads to induction of anti-oxidative defense enzymes, i.e. heme oxygenase-1 (HO1), NAD(P)H quinoneoxidoreductase 1 (NQO1), glutathione S-transferase (GSTs), SOD and glutathione peroxidase (GPXs) [35,36]. Nrf2 is controlled by its repressing protein Kelch-like ECH-associated protein 1 (KEAP1) [37]. Recent studies have shown that multiple miRNAs are capable of regulating Nrf2 and KEAP1. For example, it has been demonstrated that miR-7 inhibits KEAP1 in brain cells [38]. Also miR-141 could activate Nrf2 signaling via selectively suppressing KEAP1, that decreases UV-induced OS and apoptosis [39].

5. MiRNA biogenesis is regulated by OS signaling pathways

Given the potential role of oxidative stress components in the regulation of gene expression, OS-mediated control of miRNA biogenesis has been investigated in several studies (Table 1). OS activation, that plays a critical role in the initiation and development of cancer, seems to regulate the number of miRNAs in tumorigenesis. Notably, promoted OS is one of the primary biological signal and biochemical features that functions to promote cancer-associated miRNAs (oncomiRs) [40]. It has been shown that the expression of Dicer was down-regulated by OS in cerebromicrovascular endothelial cells (CMVECs) [41]. A line of evidence has suggested the biological role of Dicer in a feedback loop that affects ROS activation resulting in cellular homeostasis. In this view, H_2O_2 treatment leads to down-regulation of the Dicer and decreased miRNA expression [41,42].

Accumulating studies have revealed that oxidative stress system mainly modulates the expression of miRNAs via targeting various transcription and epigenetic factors [43,44]. Indeed, miRNAs affected by OS (named redoximiRs), act as regulators of target gene expression in response to oxidative stress system. For example, it has been reported that H_2O_2 treatment can cause cell degeneration by enhancing OS. These

Table 1
A number of OS mediators that could regulate miRNA expression to control ROS activation.

Oxidative stress mediator	microRNAs	Target gene/ transcription factor	Biological function	Ref
H_2O_2	miR-153	NRF2	Inhibition of antioxidant enzymes	(Narasimhan, 2014)
H_2O_2	miR-200	ZEB1	Induction of apoptosis	(Magenta, 2011)
H_2O_2	miR-141	ZEB1	Induction of apoptosis	(Brabletz,2010)
Hypoxia	miR-199	SIRT1	Induction of apoptosis	(Rane, 2009)
ox-LDL	miR-135a	TLR4	Upregulation of SOD and inhibition of ROS	(Du, 2018)
NO	miR-34, miR-203, and miR-1301	P53	Induction of apoptosis	(Li, 2015)
ROS	miR-17-92 cluster	P53	Promotion of tumor suppressive signaling	(Strickertsson, 2014)

interventions increased the expression of miR-153, targeting and reducing the level of Nrf2. A decrease in Nrf2, in turn, would elevate OS due to a reduction in the amounts of antioxidant enzymes [45]. On the other hand, various factors that generate ROS (ionizing radiation, H_2O_2, UV) are recognized to induce modulation of miRNA expression [44,46]. Multiple studies have highlighted the miRNA regulatory systems by OS signaling pathways in various cancers, indicating the critical role of OS-mediated control of miRNAs in tumorigenesis. Likewise, several miRNAs were identified to be modulated by cytotoxicity and OS, including miR-200 and miR-34a, which are induced by OS [43,44]. A miRNA profiling of human umbilical endothelial cells (HUVEC) exposed to 200 μM H_2O_2, revealed an up-regulation of miR-200 family (miR-200a, miR-200b, miR-429, miR-200c and miR-141) [44]. These miRNAs have been broadly investigated for their capacity to promote epithelial to mesenchymal transition in the tumor cells [47]. Functional investigations of possible cross-talk between OS and the aforementioned miRNAs have shown that cellular OS sensitizes tumors to chemotherapy through regulating miR-141 and miR-200a synthesis [48]. A distinctive pathway indicated the effects of OS on miRNA regulation are silent mating-type information regulation 2 homolog (SIRT1)-mediated metabolic signaling pathway. Sirtuin 1 or SIRT1 is characterized as an NAD^+-dependent class III histone deacetylase [49]. This protein is up-regulated under specific circumstances including; caloric restriction (CR) and OS [50]. As SIRT1 gene expression can be controlled at both transcriptional and post-translational levels, it is possible that underlying molecular mechanisms and effectors such as OS modulate SIRT1 through miRNAs [51]. MiR-34a was the first reported miRNA down-regulated by SIRT1 in the cellular aging-associated OS [52]. Numerous other miRNAs, including miR-141, miR-181, and miR-199, were also shown to down-regulate SIRT1 in different cells/tissues. For example, decreased expression of miR-199 in hypoxic circumstances, can lead to up-regulation of SIRT1 and reduction of apoptosis [53]. There are findings demonstrating that OS activates stress-related transcription factors such as nuclear factor-κB (NF-κB), p53, forkhead box O (FOXO), hypoxia-inducible factor (HIF), and c-jun through miRNAs regulation [54,55].

Tumor suppressor protein p53 is a major molecule in maintaining genomic stability by regulating several downstream genes involved in cell cycle arrest, apoptosis and senescence [56,57]. As a cellular transcription factor associated with OS, ROS can induce p53 expression by activating downstream genes for preserving the genome integrity [58]. Moreover, p53 is connected with miRNA processing machinery by inducing post-transcriptional maturation of different suppressor miRNAs, including miR-143, miR-16-1, and miR-145 [59]. In addition, p53 has been documented to induce a number of stress-related miRNAs such as miR-34 and miR-200 [60]. MiR-200 functions as a tumor inhibitor by suppressing the EMT process, an initial/critical step for cancer invasion and development [61]. Increased expression of miR-200 has been revealed to cause a reversal of EMT in several cancers such as gastric, pancreatic, bladder, and prostate [62]. MiR-200 may also act as a link between oxidative stress and various transcriptional factors, including FOXO family [49]. FOXO family transcriptional factors include four key proteins: FOXO1, FOXO3, FOXO4 and FOXO6. At the cytoplasmic level, downstream target genes of FOXO are implicated in the regulation of cell cycle, OS resistance, apoptosis, and cellular metabolism [63]. NF-κB is another transcriptional factor that is influenced by OS through miRNA regulatory system [64]. The elevated ROS activates NF-κB, indicating it as a redox-sensitive TF that promotes apoptosis [65]. Recent studies have also shown that up-regulation of miR-27b, attenuates OS circumstances, resulting in inhibition of lipopolysaccharide-induced activation of NF-kB [66]. Table 1 indicated a number of OS mediators that could regulate miRNA expression profile to control ROS activation.

6. OS signaling pathway is modulated by the miRNA regulatory system

In addition to the regulatory effects of OS on miRNAs activity and transcriptional status, miRNAs are reciprocally able to modulate redox homeostasis by an OS defense system. The miRNA-mediated control of the OS either as an inhibitor or promoter has also been observed. Some miRNAs may alter ROS amounts and contribute to regulate downstream biological functions by means of targeting specific genes associated with ROS generation (Table 2) [43]. A cross-talk between miRNAs and modulators of the ROS system has been proposed in which the transcription, biogenesis and maturation of miRNAs are controlled by the redox system. One of the main pathways by which miRNAs affect OS system is targeting the transcriptional factors. Various transcription factors (TFs) and kinases as key redox modulators are well-established to initiate and contribute to cellular redox signaling [66].

We have investigated some miRNAs that affect OS through TFs. For example, miR-33a down-regulates the expression of SIRT1 and SIRT6, modulating the biogenesis of lactate dehydrogenase (LDH) and ROS signaling [67]. MiR-29b also has been shown to exert a protective effect against H_2O_2 toxicity and OS through SIRT1 modulation [68]. Additionally, miR-128 sensitized colon cancer cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced cytotoxicity by inducing apoptosis [69].

Inhibition of miR-155 by targeting transcription factor Nrf2 has been confirmed to increase apoptosis and cell death [70]. MiR-125b was also shown to regulate peroxiredoxin-like 2A (PRXL2A), an antioxidant factor that protects cells from OS. Down-regulation of miR-125b inhibits the up-regulation of PRXL2A, in turn, defends the tumor cells from OS. Also, miR-125b-PRXL2A axis and downstream cascade were discovered to be an upstream effector of the Nrf2 [71]. Given the critical role of Nrf2 in the OS-related homeostasis, miR-144 has been exhibited to directly affect the cellular resistance to OS through modulation of Nrf2 expression. In this way, miR-144 overexpression causes a remarkable decrease of Nrf2 protein expression. Moreover, miR-144 can decrease antioxidant response elements (AREs)-driven gene expression and reduces cellular levels of GSH [72].

Some miRNAs may directly regulate OS-related enzymes or other molecular effectors. For example, it has been shown that several miRNAs can regulate the expression of GPXs [73]. Another study showed that miR-330-3p increased the metastasis of human cancer cells by inhibiting the manganese superoxide dismutase (hSOD2b) expression, a strong antioxidant enzyme [74]. However, other miRNAs such as miR-509-5p have been demonstrated to have tumor-suppressive effects on breast

Table 2
Several miRNAs that potentially target OS-associated effectors to regulate ROS activation in carcinogenesis.

MiRNA	Oxidant/antioxidant- mediated signaling	Target gene/proteins	Biological function	Ref
miR-15 and miR-16	Oxidant	BCL2	Inhibition of apoptosis	(Hanahan, 2011)
miR-7	Antioxidant	KEAP1	Promotion of antioxidant enzymes	(Kabaria, 2015)
miR-141	Antioxidant	KEAP1	Promotion of antioxidant enzymes	(Cheng, 2017)
miR-34a	Oxidant	SIRT1	Increase of apoptosis	(Cheng, 2017)
miR-27b	Oxidant	NF-κB	Increase of apoptosis	(Thulasingam, 2011)
miR-33a	Antioxidant	SIRT6	Elevation of LDH and ROS	(Chang, 2017)
Mir-29b	Antioxidant	SIRT1	Inhibition of H2O2-induced damage	(Hou, 2017)
miR-128	Oxidant	SIRT1	Increase of apoptosis	(Lian, 2018)
miR-155	Oxidant	Nrf2	Inhibition of apoptosis	(Chen, 2017)
miR-125b	Antioxidant	PRXL2A	Inhibition of apoptosis	(Chen, 2019)
miR-135a	Antioxidant	TLR4	Reduction of ROS, MDA, and induction of SOD	(Du, 2018)
miR-74661	Oxidant	hexose-6-p-deh and pyruvate kinase M2	Promotion of an epithelial-to-mesenchymal transition phenotype	(Gomez, 2017)
miR-921	Oxidant	GPX3	Suppression of GPXx3	(Choi, 2019)
miR-330-3p	Oxidant	hSOD2b	Suppression of SOD	(Shen, 2019)
miR-509-5p	Antioxidant	SOD2	Increase of SOD	(Song, 2017)
miR-21	Oxidant	hOGG1	Reduction of T-AOC, SOD, CAT, promotion of 8-OHdG	(Tu, 2014)
miR-30	Antioxidant	P53	Induction of apoptosis	(Wang, 2017)
miR-6785-5p and miR-642a-3p	Antioxidant	FOXO4	Increase of chemosensitivity	(Yu, 2015)
miR-10a	Antioxidant	Homeobox genes	Regulation of cell invasion /migration	(Matsushima, 2010)
miR-10b	Antioxidant	KLF4	Regulation of esophageal cancer cell invasion and migration	(Tian, 2010)

cancer cell invasion and metastasis via targeting SOD2 [75]. Increased miR-135a can suppress cell OS through modulating toll-like receptor 4 (TLR4) [76]. MiR-661 was demonstrated to have a potential relevant epigenetic regulatory role in OS and cell metabolism in colon cancer cells [77], while miR-143 increased OS in HCT116 human colon cancer cells [78].

Some miRNAs may directly affect OS-mediated enzymes or factors. For example, miR-921 suppresses the expression of glutathione peroxidase 3 (GPX3), a main antioxidant enzyme in plasma [79]. Another study showed that miR-330-3p increased metastasis of cancer cells by inhibiting of human manganese superoxide dismutase (hSOD2b) expression, a strong antioxidant enzyme [74]. However, another miRNAs such as miR-509-5p has been found to have tumor-suppressive effects on breast cancer cell invasion and metastasis via targeting SOD2 [75]. Table 2 designated several miRNAs that potentially target OS-associated effectors to regulate ROS activation in carcinogenesis.

7. Underlying molecular mechanisms of gastrointestinal carcinogenesis

The malignancies in the GI system are pathologically heterogeneous and molecular and cellular aberrations have frequently been described. GI carcinogenesis is well-known to be mediated by multifaceted genetic and epigenetic events. Genetics (various proto-oncogenes and tumor suppressor genes) and epigenetics (DNA methylation, histone modification, chromatin remodeling, and non-coding RNAs) coregulate the GI cancer initiation and progression [80]. Aberrant epigenetic modifications play a fundamental role in the formation of GI cancers [80].

Cell signaling pathways involved in GI tumorigenesis such as RAS/BRAF, PI3K/Akt, WNT/ß-catenin, JAK/STAT3, PPAR and a range of corresponding TFs have been well-studied [81]. Recently, the biological roles of non-coding RNAs particularly long non-coding RNAs (lncRNAs) and miRNAs have been increasingly identified in GI cancers. It has frequently been demonstrated that miRNAs modulate the expression of genes involved in gastrointestinal pathological conditions by affecting the cell growth, phenotype switch, fibrogenesis, ROS production, and response to stress and aging [18,82]. Recent investigations have established that numerous miRNAs may be dysregulated in GI malignancies, indicating them as tumor modulators [83]. Several studies have investigated the expression of the miRNAs in colorectal malignancies and found that miR-143 and miR-145 function as potential regulators in tumorigenesis [84]. In this regard, it has also been confirmed that some of miRNAs exert their biological roles in cancers through modulating OS factors. For example, miR-210 (with a HIF-1α-binding site in its promoter) was revealed to be remarkably up-regulated in hypoxia conditions and increase tumorigenesis in colon, pancreatic, and breast cancers [85]. It has been substantiated that hypoxia leads to angiogenesis in the initiation and development of cancers. In contrast, a number of miRNAs have protective effects on carcinogenesis. For example, recent studies have demonstrated that miR-143 overexpression could promote cell apoptosis, and decrease colon tumor development, *in vivo* [86]. In the same way, miR-145 up-regulation has been reported to modulate apoptosis, and suppress colon cancer cell growth and proliferation [87,88].

8. Cross-talk between oxidative stress signaling and miRNAs regulatory systems in GI cancers

Given the pivotal roles of a variety of TFs, ROS and noncoding RNAs in GI cancers, explaining the relationship between these factors can increase insight into molecular identification as well as targeted therapies [81]. As mentioned above, OS and miRNA axis and corresponding signaling pathways may be considered as fundamental pathways in GI cancer development (Fig. 1). Increasing evidence suggests that continuous OS can induce oncomiRNA-associated cascades leading to gastrointestinal diseases and carcinogenesis. Reciprocally, miRNA network regulates OS signaling effectors and consequent molecular events involved in GI cancers (Fig. 1). In the following, we review the interaction between OS and miRNA regulatory systems in gastrointestinal cancers. In this regard, we point out the function of miRNAs which target OS systems and discuss the cross-talk between OS and miRNAs during GI tumorigenesis.

8.1. Colorectal Cancer

Given that the underlying mechanisms associated with both miRNAs

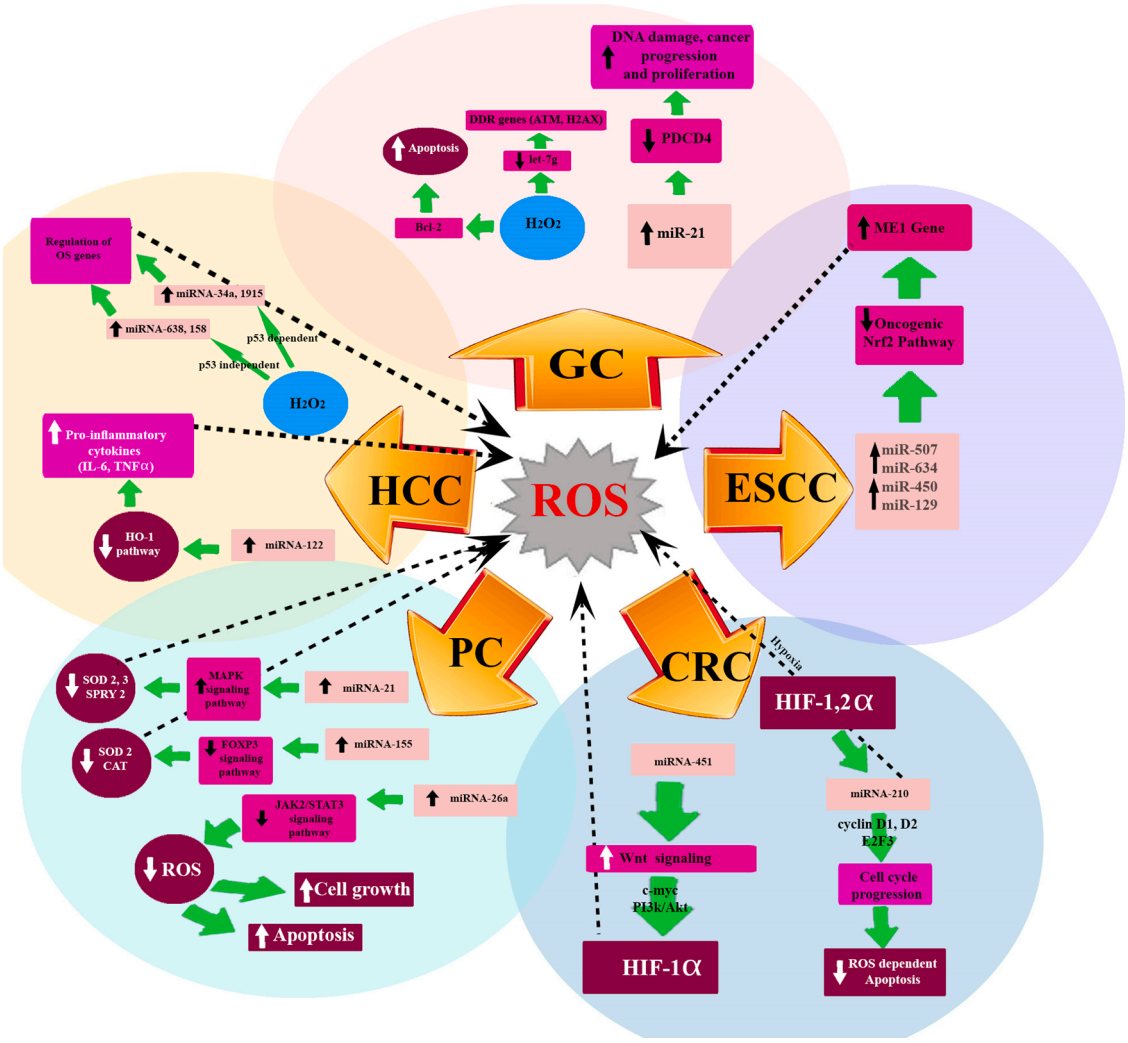

Fig. 1. Schematic graph illustrating molecular cross-talking between ROS production and the miRNA regulation in the underlying mechanisms of GI cancers. Molecular mechanisms of ROS activation may be involved in the regulation of the miRNA expression in GI cancers by affecting the miRNA biogenesis and transcription. ROS activation also can increase or inhibit transcriptional factors (P53, NFκB, HIF1α, c-Myc and NRF2) and epigenetic factors to regulate miRNAs in GI carcinogenesis. Reciprocally, miRNAs can modulate OS system through targeting the upstream genes and corresponding signaling pathways. Therefore, a potential cross-talking between ROS, TFs and miRNAs contribute to regulate cell growth, cell cycle, apoptosis, tumor development and progression.
* ROS; reactive oxygen species, GI; gastrointestinal, TF; transcription factor.

and OS system were described in colorectal cancer (CRC), it is fundamental to identify their possible role of cross-talking regarding tumorigenesis [89,90]. Expression analysis of miRNAs and functional examinations in colon cancer cells have shown that key cellular pathways, such as cell apoptosis, response to OS and protein folding are regulated by miRNA system [89]. GRP94, SOD1 and annexin II (ANXA2) proteins are characterized as corresponding targets down-regulated by miR-143 or miR-145 [78]. These proteins are involved in OS signaling pathways and apoptosis regulation in tumor cells. In addition, miRNA-661 has been proposed to play a critical role as an epigenetic modulator of colon cancer cell metabolism. MiR-661 promotes ROS, particularly mitochondria-derived SO contributes in epithelial-mesenchymal transition (EMT) phenotype in non-metastatic colon cancer cells. This signaling axis also may cause an increased tumor cell sensitivity to OS [77]. MiR-34 expression in CRC cells is remarkably associated with the amount of inducible nitric oxide synthase (iNOS). Elevated NO may be as a an important factor in the selection of cells with a low level of p53-dependent miRNAs that are responsible for tumor development and progression [91].

in vitro studies showed that antioxidant and anti-inflammatory drugs such as curcumin [92] and Ethyl 2-((2,3-bis(nitrooxy)propyl) disulfanyl)benzoate (GT-094) [93] inhibit cell proliferation and induce apoptosis through downregulating miRNA-27a and inducing zinc finger and BTB domain containing 10 (ZBTB10). Both *in vitro* and *in vivo* studies have demonstrated that miR-124 functions as a tumor inhibitor and a regulator of energy homeostasis through a polypyrimidine tract-binding protein 1 (PTB1), pyruvate kinase muscles 1 and 2 (PKM1and PKM2) feedback cascade in human colorectal tumor cells [94]. MiR-210 up-regulation was found to promote ROS synthesis in colorectal tumor cells. MiR-210 can down-regulate mitochondrial iron-sulfur cluster scaffold homologue and contribute to mitochondrial activity in OS activation [95]. MiR-210 was also established to induce OS activation under hypoxic condition, resulting in an invasive and progressive CRC [89]. In addition, miR-210-induced apoptosis by increased ROS has been described in CRC [89]. Furthermore, up-regulation of miR-141 and miR-200a was revealed to regulate ROS production and tumor proliferation by targeting p38a (Fig. 1) [96].

8.2. Gastric Cancer

ROS production has been reported to cause a dysregulated expression of miRNAs in gastric cancer (GC). According to recent reports,

epigenetic elements play a major role in gastric carcinogenesis during OS activation (Fig. 1). ROS may promote the methylation of several miRNA genes, such asmiR-329, miR-199, miR-145-5p, miR-125, and miR-362-3p, resulting in promoting GC progression, [97–99]. In addition miRNAs and Circular RNAs (circRNAs) expression profles has been revealed to be a potential biomarkers involved in GC [100]. Moreover, in helicobacter pylori-induced GC, reduced expression of miR-328 has been reported to be involved in ROS generation [101]. In GC, hypoxia can also change the expression of miRNAs. For instance, miR-495 was demonstrated to be up-regulated in two gastric cell lines, SNU484 and SNU5, under hypoxic circumstances [102]. Overexpression of miR-21 can decrease total anti-oxidation competence (T-AOC), SOD and CAT, but increases 8-oxo-deoxyguanosine (8-OHdG) and human 8-oxoguanine DNA N-glycosylase 1 (hOGG) mRNA. Moreover, the expression levels of miR-21 have been found to be negatively associated with programmed cell death 4 protein (PDCD4) in gastric cancer cells [103]. Hsa-let-7 g also exerts an anti-tumor effect which is induced by ox-LDL. This miRNA promotes the sensitivity of gastric cancer cells to OS by indirect inhibition of DNA damage response genes [104].

Interestingly, gastric cancer cell apoptosis was observed to be mediated by a group of antioxidants and miR-143, indicating miR-143 could increase the chemical sensitivity of the antioxidants through autophagy suppression [105]. Bacterial infection and ROS stimulation can down-regulate the expression of miR-17-92 cluster in gastric cancer cell lines [106]. The miR-17-92 cluster is an instance of miRNAs with both oncogenic and tumor suppressive effects, based on cancer type. This group of miRNAs was found to be down-regulated in DNA damage via a p53-dependent process or due to excessive ROS [107,108]. Furthermore, down-regulation of miR-30 in gastric cancer has reported to elevate ROS production which is suppressed by p53. Therefore, miR-30 was concluded to act as a potential suppressor miRNA through p53/ROS-mediated modulation of the mitochondrial apoptotic pathway in GC [109]. Moreover, downregulation of miR-6785-5p and miR-642a-3p and subsequent enhancing FOXO4 expression were shown to increase chemosensitivity of resistant gastric carcinoma cells [110]. In several GI cancers, especially GC and CRC, inflammation and OS are frequently well-depicted to contribute to the development and progression of cancer. Peroxisome proliferator-activated receptor gamma (PPARγ) has been reported to be down-regulated through inflammation and OS in GC and CRC [111]. Conversely, the WNT/β-catenin pathway is commonly activated in these cancers. A number of downstream signaling pathways and related target genes such as c-Myc, cyclin D1 and HIF-1α are implicated in the development of GC and CRC. Transcription factor NFκB, as and activator of various inflammatory and growth factors, can promote the ROS synthesis via inducing nitric oxide synthase enzyme. ROS activation can reciprocally motivate the expression and activation of inflammatory factor NFκB, activator protein-1, HIF-1α, stimulating the canonical WNT pathway [111]. Moreover, ROS was confirmed to trigger the phosphatidylinositol 3 kinase/protein kinase B (PI3K/Akt) signaling pathway in the malignancies. Aforementioned signaling network concerning the WNT/β-catenin pathway and PPARγ in ROS regulation was observed to be modulated by miRNA systems [111]. So, up-regulation of miR-451 can promote WNT/β-catenin signaling pathway and several downstream signaling, including c-Myc and PI3K/AKt in GC. The activation of these signaling pathways may activate HIF-1α that stimulates the ROS synthesis [111].

8.3. Hepatocellular Cancer

The critical role of miRNAs in the multiple stages of chronic liver complications in the development of liver cancer has been identified [112,113]. Recent findings confirmed the effect of ROS-mediated oxidative DNA damage to hepatocellular carcinoma (HCC), and in this way, dys-regulation of some miRNAs was described. For example, over-expression of miR-92, with a role in both the apoptotic process and cellular proliferation pathways, was associated with increased risk of HCC [114]. In addition, recent researches demonstrated a remarkable positive association between miRNA-92 expressions and Hepadna virus-associated carcinogenesis in HCC tissues. Besides, studies showed that miRNA-122a, miRNA-195, miRNA-199b, and miRNA-199a are down-regulated in the most (55 %–70 %) of HCCs, while miRNA-222 is up-regulated in the malignancy [114,115]. MiRNAs also were recognized as key players to be involved in the regulation of iron homeostasis in pathology of HCC [116]. Accordingly, investigation of OS parameters and miRNAs and the corresponding molecular mediators were proposed as a new strategy for HCC diagnosis and prognosis. In this regard, it was recognized four OS-responsive miRNAs, which were modulated by a p53-independent (miR-638 and miR-150-3p) manner and p53-dependent pathway (miR-1915-3p and miR-34a-5p) [117]. As mentioned earlier, miR-210 induces under hypoxic conditions and can function as an oncomiR in tumorigenesis. It was found that transcription factor HIF-1α can regulate the miR-210 expression by binding to the miR-210 promoter via hypoxia response element (HRE). On the other hand, some findings show ROS activation is connected to the telomerase activity in HCC. The interplay between ROS regulation and telomerase activity is related to HIF-1α signaling (Fig. 1). So that, HIF-1α was revealed to induce and promote corresponding downstream signaling pathway triggered by ROS [118].

ROS exposure has also been shown to be correlated with oncogenic signals such as those transduced by c-Myc and Ras. c-Myc, a well-known oncogene, is involved in tumor growth, migration, invasion and metastasis through the regulation of gene expression. c-Myc activation induces DNA damage in normal human fibroblasts. This effect has been correlated with ROS generation [119]. The expression levels of miR-17-92 were remarkably inhibited by triptolide in a c-Myc-dependent manner, which resulted in the induction of target genes, including phosphatase and tensin homolog (PTEN), bcl-2 interacting mediator (BIM) and p21, in HCC cells [120].

8.4. Esophageal Cancer

Accumulating investigations indicated dysregulation of miRNAs in esophagus pathological conditions. It was hypothesized that miRNAs expression could be used to distinguish patients who have a high risk for esophageal dysplasia, Barrett esophagus, esophageal cancer (EC), and esophageal squamous cell carcinoma (ESCC) [121]. It has also been identified that miR-205 and miR-10a are remarkably changed, and possibly have pivotal functions in the pathogenesis of ESCC. As an outcome of the mechanistically investigation on miR-205, it was validated that this miRNA could regulate the epithelial-mesenchymal transition program by decreasing the levels of E-cadherin. This biological event is characterized as an important miRNA regulation of ESCC in which representative E-cadherin inhibitors, zinc finger E-box binding homeobox 1(ZEB1) and ZEB2 are suppressed. In the same way, miR-10a is recognized as a tumor inhibitor owing to regulate cell invasion/migration via affecting homeobox genes [122]. MicRNA-10b Also reduces cell invasion and migration by inhibiting Kruppel-like factor 4 (KLF4; a known tumor suppressor gene which inhibits cell invasion and migration) in esophageal cancer cell lines [123].

However, the biological role of oxidative stress and ROS activation in ESCC has not been well investigated. One study examined the underlying molecular mechanisms of oxidative stress induced by H_2O_2 in the ESCC cells. The results of this study showed that H_2O_2 could promote cell death in tumor cells via the activation of poly (ADP-ribose) polymerase 1 (PARP1), Caspase 3, and Caspase 9. Hence, the findings suggested that H_2O_2 may be involved in mitochondrial dysfunction by promoting the ROS synthesis, regulating cell growth [124]. Another study showed that several suppressor miRNAs, including miR-507, miR-634, miR-450a, and miR-129-5p can target/inhibit the Nrf2 pathway. Given the pivotal function of the Nrf2 signaling pathway in ROS and antioxidant responses, a miRNA-mediated ROS regulation may be hypothesized to involve in ESCC tumorigenesis.

8.5. Pancreatic Cancer

MiRNAs have been associated with various cellular processes in pancreatic cancer (PC) development and progression. MiRNAs have confirmed to be modulated by a metabolic function of the pancreas, in parallel, miRNAs can regulate and change metabolic function (Fig. 1). The corresponding signaling networks are served as key important underlying mechanisms in pancreatic neoplasms [125]. For instance, overexpression of miR-155 leads to suppression of Foxo3a, reducing most important antioxidants enzymes such as superoxide dismutase (SOD2) and catalase (CAT), increasing the ROS generation and pancreatic cell proliferation [126]. Additionally, phosphorylation of the signal transducer and activator of transcription 3 (STAT3) was also down-regulated by miR-216a, whereas the anti-miR-216a treatment had an opposite effect. Treatment of pancreatic cancer cells with miR-216a significantly inhibited cell growth and promoted cell apoptosis. In addition, the downstream genes of JAK2/STAT3, survivin and X-linked inhibitor of apoptosis protein, as anti-apoptotic genes, were also decreased by miR-216a. Moreover, miR-216a overexpression can noticeably inhibit the JAK2/STAT3 signaling pathway and xenograft tumor growth *in vivo*. Compared with miR-216a treatment, anti-miR-216a treatment exhibited opposite effects throughout the entire experiment, confirming the inhibitory effect of miR-216a on pancreatic cancer by regulating the JAK2/STAT3 signaling pathway. The results provided evidence that miR-216a targeting JAK2 negatively regulated the development of pancreatic cancer cells and may be used to develop a miRNA-based therapeutic strategy against pancreatic cancer [127].

Similar to some other cancers, several TFs such as c-Myc and SIRT1 were found as potential targets for miRNAs in PC. For example, up-regulation of miR-494 was shown to suppress pancreatic cancer cell proliferation through stimulation of apoptosis, G1-phase arrest, and senescence [128]. Furthermore, an OS-mediated miR-21 up-regulation was reported to increase cell migration in pancreatic cancer cells. It has been demonstrated that miR-21 promotes ROS generation through activating the mitogen-activated protein kinase (MAPK) pathway and inhibiting SOD2, SOD3 and sprouty homolog 2 (SPRY-2) expression [129].

9. Conclusion

Since the discovery of miRNAs, it has been shown that these molecules play a significant role in GI cancer pathology. On the other hand, numerous investigations have shown a critical function of oxidative stress in GI cancers. Indeed, it has been well-known that the development and progression of GI cancers are mediated by both OS and miRNAs. In this view, several studies have also been performed to illuminate the cross-talking between the OS system and miRNAs and potential ROS/miRNA axis as molecular mechanisms underlying GI tumorigenesis. ROS transcriptionally or post-transcriptionally modulate the expression of miRNAs, and miRNAs target the key genes to regulate ROS in OS-derived tumors. Accumulating evidence indicated a reciprocal connection between OS signaling pathways and miRNA regulatory machines in GI cancer development and progression. In this review, we illustrated the function of miRNAs which target OS systems and described the biological cross-talk between OS systems and miRNAs in the GI system. Understanding the molecular mechanisms in which these systems reciprocally be regulated would improve our pathophysiological insight into GI carcinogenesis, helping in future cancer therapeutics. Our results indicated that cross-talk between miRNAs and OS can affect GI carcinogenesis through modulating the genes involved in transcriptional and post transcriptional regulation such as BCL2, KEAP1, NF-κB, SIRTs, Nrf2, PRXL2A, TLR4, hOGG1, FOXO4, Homeobox genes, ZEB1, p53 and KLF4.

Recently, cancer therapy approaches focusing on miRNA and ROS have received special attention, so, the discovery of OS-responsive miRNAs may provide opportunities for developing novel anticancer strategies to overcome OS-mediated carcinogenesis. However, there are still a lot of therapeutic boundaries for OS-mediated cancers owing to the dual roles of ROS in tumorigenesis.

Author contributions

A. A, H. M. M, J. H and M. M contributed to the conception or design of the work. R. R, S.M. A and M. M completed a literature review and contributed to preparation of manuscript draft. All authors confirmed the final version for submission.

Author statement

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of Competing Interest

The authors report no declarations of interest.

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